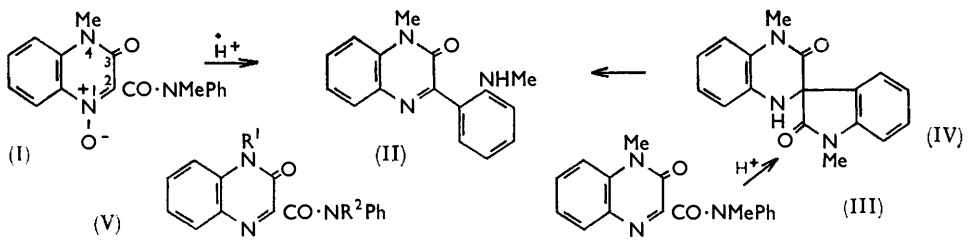
23. *The Rearrangement of Certain Quinoxalinecarboxyanilides to Spiro-compounds.*

By M. S. Habib and C. W. Rees.

3,4-Dihydro-4-methyl-2-(*N*-methyl-*N*-phenylcarbamoyl)-3-oxoquinoxaline (III) isomerises to the spiro-lactam (IV), very rapidly in concentrated sulphuric acid at 0° and more slowly in hot ethanolic hydrogen chloride. The mechanism of this rearrangement is very similar to that previously reported for its 1-oxide (I) though the spiro-lactam formed here is not further decomposed; the scope of this rearrangement is similarly limited.

An intermediate of the type postulated previously for the *N*-oxide rearrangement in sulphuric acid, the hydroxyamino-spiro-lactam (IX), has now been isolated by making use of the slower reaction in ethanolic hydrogen chloride.

In earlier papers [1] it was shown that the very rapid conversion of the *N*-oxide (I) into the amine (II) by ice-cold sulphuric acid proceeds by intramolecular electrophilic substitution of the anilide ring by $C_{(2)}$ of the quinoxaline ring. Although the *N*-oxide group is partly responsible for creating the electrophilic centre at $C_{(2)}$ and is necessary for subsequent decarboxylation and dehydration by a cyclic mechanism,[1] it was to be expected that the parent base (III) would also be sensitive to acid. This was found to be so; in ice-cold sulphuric acid it immediately developed a deep red colour like its 1-oxide (I), but without evolution of carbon dioxide, and was rapidly converted into the isomeric spiro-lactam (IV), though in low yield. Boiling ethanolic hydrogen chloride effected this conversion more slowly, but almost quantitatively.

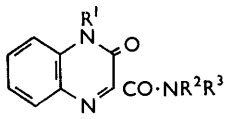


The structure of the spiro-lactam (IV) followed from its mode of formation, appearance of an N–H absorption band (3300 cm.$^{-1}$) and a shift of the amide carbonyl absorption to 1712 cm.$^{-1}$ characteristic of *N*-methyloxindoles,[2] and from its conversion into 3,4-dihydro-4-methyl-2-*o*-methylaminophenyl-3-oxoquinoxaline (II) by prolonged boiling with hydrochloric acid. The last reaction involves hydrolysis of the oxindole ring, decarboxylation, and oxidation of the dihydro-derivative of (II) so formed. The 6-chloro-derivative of the spiro-lactam (IV) has been prepared from the oxide (I) and ethanolic hydrogen chloride and its structure established by Clark-Lewis and Katekar; [3] the two carbonyl absorption frequencies of our compound were very similar to those reported [3] for the chloro-derivative.

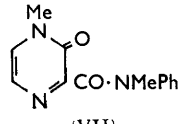
3,4-Dihydro-4-methyl-2-(*N*-phenylcarbamoyl)-3-oxoquinoxaline (V; R^1 = Me, R^2 = H) and 3,4-dihydro-2-(*N*-methyl-*N*-phenylcarbamoyl)-3-oxoquinoxaline (V; R^1 = H, R^2 = Me) rearranged similarly in cold concentrated sulphuric acid or hot ethanolic hydrogen chloride to the corresponding spiro-lactams. In sulphuric acid the former compound gave a sulphonated derivative; as expected, the product from the latter yielded spiro-lactam (IV) on methylation. Rearrangement of the 1-oxides of these two anilides

[1] Habib and Rees, *J.*, 1960, 3371, 3384, 3386.
[2] Wenkert, Bose, and Reid, *J. Amer. Chem. Soc.*, 1953, **75**, 5514.
[3] Clark-Lewis and Katekar, *J.*, 1959, 2825.

could not be accomplished as all our attempts to prepare the oxides were unsuccessful.[1] In contrast to the rapid reaction of these anilides, the quinoxalines (VIa—d) and the pyrazine (VII) were all unchanged by concentrated sulphuric acid at room temperature.[1] Thus the limited scope of this rearrangement is very similar to that of the corresponding

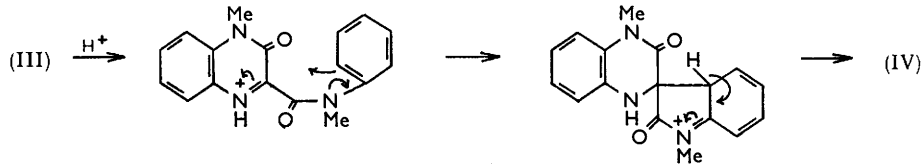


(VI) a: R^1 = Me, R^2 = R^3 = H
b: R^1 = R^2 = R^3 = Me
c: R^1 = R^2 = Me, R^3 = 2,6-$C_6H_3Me_2$
d: R^1 = R^2 = Me, R^3 = *p*-$NO_2 \cdot C_6H_4$



(VII)

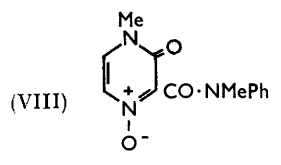
1-oxides and a similar mechanism is indicated. The quinoxaline-2-carboxyamide must be an anilide where the phenyl ring has a free *ortho*-position, and electron withdrawal from this ring inhibits the reaction. The annexed mechanism is therefore proposed:



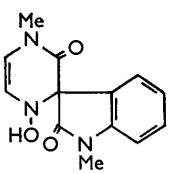
The initial driving force, as in the oxide rearrangement, is intramolecular attack of the neighbouring anilide *ortho*-position by the highly developed electrophilic centre at $C_{(2)}$ in the conjugate acid.

Spiro-lactams such as (IV) are closely related in structure to those postulated as intermediates in the *N*-oxide rearrangements, differing only in having an $N_{(1)}$–H rather than an $N_{(1)}$–OH group. However, such intermediates could not be isolated from the *N*-oxide reactions in sulphuric acid, or by direct oxidation of spiro-lactams such as (IV) with hydrogen peroxide and acetic acid. When the anilides were found to rearrange much more slowly in ethanolic hydrogen chloride, isolation of a 1-hydroxyl compound was attempted. This was accomplished with the pyrazine *N*-oxide (VIII) which, when heated with ethanolic hydrogen chloride for 3 hr., gave the hydroxyamino-spiro-lactam (IX). The structure of this product followed from its mode of formation and elementary analysis, its reduction of ammoniacal silver nitrate to a silver mirror, and its infrared spectrum. It absorbed strongly at 3320 (OH, not phenolic), 1665 (six-membered cyclic lactam carbonyl), 1710 (*N*-methyloxindole carbonyl), and 755 cm.$^{-1}$ (1,2-disubstituted benzene).

The pyrazine *N*-oxide (VIII) rather than the quinoxaline *N*-oxide (I) was chosen for conversion into the hydroxyamino-spiro-lactam, since the latter oxide with ethanolic



(VIII)



(IX)

hydrogen chloride was shown by Clark-Lewis and Katekar [3] to give a chloro-compound; they postulated that this was formed *via* the quinoxaline hydroxyamino-spiro-compound analogous to the pyrazine (IX) which we have isolated. The pyrazine *N*-oxide (VIII) also differed from the quinoxaline *N*-oxide (I) in being inert towards boiling acetyl chloride.

Experimental

General experimental procedure, preparation of the compounds, and recovery of the amides unaffected by sulphuric acid have been described.[1]

Treatment of Anilides with Sulphuric Acid.—The finely powdered anilide was added in small portions to ten times its weight of vigorously stirred ice-cold sulphuric acid, the solution was left for 5 min., then poured on ice, and the precipitate was collected, washed with water, and crystallised from ethanol. The products showed a marked tendency to separate with solvent of crystallisation, as found by Clark-Lewis and Katekar.[3]

(*a*) 3,4-Dihydro-4-methyl-2-(*N*-methyl-*N*-phenylcarbamoyl)-3-oxoquinoxaline (III) (8 g.) gave *1,2,3,4,2′,3′-hexahydro-4,1′-dimethyl-3,2′-dioxoquinoxaline-2-spiro-3′-indole ethanol solvate* (IV) (3·5 g.), m. p. 243° (Found: C, 67·3; H, 6·2; N, 12·5. $C_{17}H_{15}N_3O_2,C_2H_5{\cdot}OH$ requires C, 67·2; H, 6·2; N, 12·4%). Ethanol was removed by drying to constant weight at 150°. (Found: C, 69·3; H, 5·1; N, 14·3. $C_{17}H_{15}N_3O_2$ requires C, 69·6; H, 5·2; N, 14·3%).

(*b*) 3,4-Dihydro-2-(*N*-methyl-*N*-phenylcarbamoyl)-3-oxoquinoxaline (V; R^1 = H, R^2 = Me) (6 g.) gave *1,2,3,4,2′,3′-hexahydro-1′-methyl-3,2′-dioxoquinoxaline-2-spiro-3′-indole hydrate* (2 g.), m. p. 244° (Found: C, 64·4; H, 5·1; N, 14·0. $C_{16}H_{13}N_3O_2,H_2O$ requires C, 64·6; H, 5·1; N, 14·1%). Methylation of this by methyl sulphate and 2N-sodium hydroxide for 16 hr. gave the spiran (IV), m. p. 243° (from ethanol) not depressed on admixture with that described under (*a*).

(*c*) 3,4-Dihydro-4-methyl-2-(*N*-phenylcarbamoyl)-3-oxoquinoxaline (V; R^1 = Me, R^2 = H) gave *1,2,3,4,2′,3′-hexahydro-4-methyl-3,2′-dioxoquinoxaline-2-spiro-3′-indole-x-sulphonic acid dihydrate*, m. p. 267—270° (Found: C, 48·8; H, 4·5; S, 7·3. $C_{16}H_{13}N_3O_5S,2H_2O$ requires C, 48·6; H, 4·3; S, 8·1%). This product gave a crystalline precipitate with *S*-benzylthiouronium chloride.

Treatment of Anilides with Ethanolic Hydrogen Chloride.—The anilide (1 g.), in ethanol (25 ml.) saturated with hydrogen chloride, was heated under reflux for 2 hr. Ethanol was removed under reduced pressure, water was added, and the precipitate was crystallised from ethanol.

(*a*) 3,4-Dihydro-4-methyl-2-(*N*-methyl-*N*-phenylcarbamoyl)-3-oxoquinoxaline (III) gave the spiran (IV) (1 g.), m. p. 243°, not depressed on admixture with the spiran prepared by rearrangement in sulphuric acid.

(*b*) 3,4-Dihydro-2-(*N*-methyl-*N*-phenylcarbamoyl)-3-oxoquinoxaline (V; R^1 = H, R^2 = Me) gave 1,2,3,4,2′,3′-hexahydro-1′-methyl-3,2′-dioxoquinoxaline-2-spiro-3′-indole (0·8 g.), m. p. 244°, not depressed on admixture with that prepared by rearrangement in sulphuric acid. The infrared spectra (in Nujol mull) of these two spiro-lactams and that from 3,4-dihydro-4-methyl-2-(*N*-phenylcarbamoyl)-3-oxoquinoxaline (V; R^1 = Me, R^2 = H) showed strong carbonyl absorption at 1712, 1718, and 1724 $cm.^{-1}$ (*N*-methyloxindole amide carbonyl) and N–H absorption at 3300, 3280, and 3280 $cm.^{-1}$ respectively.

3,4-Dihydro-4-methyl-2-o-methylaminophenyl-3-oxoquinoxaline (II).—1,2,3,4,2′,3′-Hexahydro-4,1′-dimethyl-3,2′-dioxoquinoxaline-2-spiro-3′-indole (IV) (1 g.), concentrated hydrochloric acid (10 ml.), and ethanol (10 ml.) were heated under reflux for 6 hr. Ethanol was removed under reduced pressure and the residue poured into water and basified with sodium hydroxide. The precipitate crystallised from aqueous methanol, to give the amine (II) (0·1 g.), m. p. and mixed m. p. 142—144°. The infrared spectrum (in Nujol mull) was identical with that of the authentic specimen.

1,2,3,4,2′,3′-Hexahydro-1-hydroxy-4,1′-dimethyl-3,2′-dioxopyrazine-2-spiro-3′-indole (IX).—3,4-Dihydro-4-methyl-2-(*N*-methyl-*N*-phenylcarbamoyl)-3-oxopyrazine-1-oxide (VIII) (1 g.) in ethanol (25 ml.), saturated with hydrogen chloride, was heated under reflux for 3 hr. The volume was reduced to 10 ml. and the solution refrigerated overnight. The crystalline chlorine-free solid which separated recrystallised from ethanol to give colourless cubes of the *spiro-indole* (IX) (0·75 g.), m. p. 186—188°, depressed to 160—165° on admixture with starting material (Found: C, 60·2; H, 4·9; N, 16·4. $C_{13}H_{13}N_3O_3$ requires C, 60·1; H, 5·0; N, 16·3%).

We thank Professor D. H. Hey, F.R.S., for his interest and encouragement.

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[*Received, August 8th,* 1961.]